

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-256.2CIPWO		FOR FURTHER ACTION		See Form PCT/IPEA416
International application No. PCT/IB2004/000008		International filing date (day/month/year) 06.01.2004	Priority date (day/month/year) 11.04.2003	
International Patent Classification (IPC) or national classification and IPC C07D209/52				
Applicant RANBAXY LABORATORIES LIMITED et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 10.05.2004		Date of completion of this report 29.06.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Schuemacher, A Telephone No. +49 89 2399-7818 		

**INTERNATIONAL PRELIMINARY REPORT
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-22 as originally filed

Claims, Numbers

1-21 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 4-7
because:
 - ☒ the said international application, or the said claims Nos. 4-7 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 - ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-21
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-21
Industrial applicability (IA)	Yes: Claims	1-3,8-21
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4-7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty, Article 33(1) and 33(2) PCT:

Reference is made to the following documents:

- D1: EP-A-0 823 423 (BANYU PHARMA CO LTD) 11 February 1998
- D2: EP-A-0 843 141 (GEA WAERME UND UMWELTTECHNIK G) 20 May 1998
- D3: WO 02/053564 A (ALMIRALL PRODESFARMA AG) 11 July 2002
- D4: WO 02/04402 A (BANYU PHARMA CO LTD) 17 January 2002
-& EP 1 302 458 A (BANYU PHARMACEUTICAL CO, LTD.) 16 April 2003

As D4 is a international patent application in Japanese and in order to avoid any misunderstanding, the family member document EP1302458 is used to assess the novelty and inventive step of the present application.

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the 6-substituted 3-azabicyclo[3.1.0]hexane compounds of formula (I), appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The claimed compounds differ from the compounds of D1-D3 on account of the 3-azabicyclo[3.1.0]hexane ring. The compounds of D4 may contain an azabicyclic ring, however not a 3-azabicyclo[3.1.0]hexane ring.

Hence, claims 1-21 are novel over D1-D4 and the requirements of Article 33(2) PCT are considered to be met.

2. Inventive step, Article 33(1) and 33(3) PCT:

The Applicant appears to have set himself the task of making available further muscarinic receptor antagonists, useful for the treatment of respiratory, urinary and gastrointestinal diseases, see first paragraph on top of p.1.

All four documents D1-D4 relate to muscarinic antagonists, but considering the chemical structure, it is considered that D4 is the closest prior art document.

The claimed compounds differ from those of D4 on account of the 6-substituted 3-azabicyclo[3.1.0]hexane ring. However, D4 discloses also in claim 22 compounds of formula (II), which exhibit highly selective antagonism to muscarine M3 receptor (see p.4, l.18-20). From claim 22 and 27 of D4 it is clear that the group Ap can vary from pyrrolidine, piperidine, tetrahydropyridine or even a 8-azoniabicyclo[3.2.1]-octane without loss of the muscarinic antagonistic activity. Even in D3, the corresponding nitrogen-containing heterocycle is a quinuclidine ring.

Thus, it would be obvious to the skilled person, looking for further muscarine M3 receptor antagonists, to replace the nitrogen-containing heterocycle of the compounds of formula (II) in D4 by another one like 3-azabicyclo[3.1.0]hexane. The present claimed compounds can therefore be considered as obvious alternatives of those disclosed in D4.

The problem underlying the present application is therefore to be seen the provision of compounds having an unexpected advantageous effect with regard to the compounds of D4. In the present application p.22, it is stated that the claimed compounds possess the alleged activity, but there is no evidence for a surprising effect compared to the already known muscarine receptor antagonists. Such evidence could take the form of, for example, comparative data between a representative set of compounds of the present application and those of D4, which present maximal structural similarity with the claimed compounds.

An inventive step can therefore not be recognized as it has not yet been shown by appropriate information that the claimed subject-matter includes any unexpected or surprising effects.

In the absence of evidence demonstrating an unexpected effect of a representative set of compounds as claimed, Article 33(3) PCT cannot be considered to be satisfied.

3. industrial applicability:

For the assessment of the present claims 4-7 on the question whether they are industrially

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applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004/004629	15.01.2004	08.07.2002	
WO2004/018422	04.03.2004	23.08.2002	

These documents are related to 6-substituted 3-azabicyclo[3.1.0]hexane compounds as muscarinic receptor antagonists.